REMARKS

Claims 1, 3-8, 20, 22-25, 51 and 52 are pending in the present application. By virtue of this response, claim 3 has been cancelled; and claim 1 has been amended. Accordingly, claims 1, 4-8, 20, 22-25, 51 and 52 are currently under consideration.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Statement of the Substance of the Interview

Applicants' representative Jie Zhou wishes to thank Examiner Kim for the time spent during the telephonic interview on January 14, 2009 and helpful comments provided. The Examiner and the Applicants' representative discussed rejections in the Office Action. In accordance with MPEP 713.04, this response contains a summary of the substance of the interview.

Double Patenting

A. Claims 1, 3-8, 20, 22-25, 51 and 52 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 B2 ("the '432 patent") in view of US 2004/109243A1, for the reasons set forth in the office action mailed on 6/4/08.

Applicants respectfully note that the publication number for the second reference cited by the Examiner seems to be US 2004/0191243, not US 2004/109243, according to the Office Action dated January 5, 2007. Accordingly, this rejection is addressed based on the disclosure in US 2004/0191243 ("the '243 application"). Applicants respectfully request clarification from the Examiner.

Applicants respectfully traverse this rejection, and respectfully submit that claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of the '432 patent in view of the '243 publication.

The pending claims in the present application recite a rhuMAbE25 formulation containing about 150 to 260 mg/ml antibody, arginine-HCl (100 to 200 mM), histidine (10 to 100 mM), polysorbate (0.01 to 0.1%), and pH (from 5.5 to 6.0). This formulation is different from the claimed formulation in the '432 patent. The formulation in claim 1 (from which claims 2-4, 7-13, and 22-27 depend) in the '432 patent comprises about 80 to about 130 mg/ml protein and a salt and/or buffer of at least about 150 mM. The formulation in claim 31 (from which claims 32-34, 37-42, 48, 51-56, 58 and 59 depend) in the '432 patent comprises about 80 to about 130 mg/ml protein, a salt and/or buffer of at least about 150 mM, and a pH of about 4.2 to 5.3 or 6.5 to about 12.0.

Applicants respectfully submit that the protein concentration range in claims of the present application is distinct from the protein concentration range recited in the '432 patent. Applicants disagree with the Examiner that the antibody concentration range of about 80 to about 130 mg/ml can be interpreted to encompass the antibody amount of "160-260 mg/ml" [sic, about 150 to 260 mg/ml] in view of claim 20 in the '432 patent. The Examiner asserts that claim 20 in the '432 patent encompasses a range of antibody higher than that specified in claim 1 of the '432 patent.

Applicants respectfully submit that the Examiner is misreading claim 20 of the '432 patent, especially all of the limitations in claims 19 and 1. The claim scope of a dependent claim must be read with all of the limitations that also appear in the depending claims. MPEP 608.01(n). Claim 20 specifies that the reconstituted protein concentration is about 2-40 times greater than the pre-lyophilized protein concentration. Claim 19 explicitly states that the claimed formulation is reconstituted, while claim 1 specifies that the claimed formulation has a protein concentration of about 80 to about 130 mg/ml. Thus, the protein concentration in the claimed formulation (i.e., the reconstituted concentration) is about 2-40 times greater than the pre-lyophilized protein concentration, and the protein concentration of the claimed formulation is about 80 mg/ml to 130

mg/ml as specified in claim 1. Claim 20 does not support an interpretation that claim 1 encompasses the antibody concentration of about 150 mg/ml to 260 mg/ml.

Although claims in the '432 patent recite that the protein concentration is about 80 mg/ml to about 130 mg/ml. The term "about" as defined in Oxford English Dictionary, means nearly, approximately, not many more or less, a copy of the relevant pages in the Oxford English Dictionary are attached under Appendix A. The difference between 130 mg/ml and 150 mg/ml is at least 13%. Therefore, a protein concentration of about 130 mg/ml would not be considered to overlap with a protein concentration of about 150 mg/ml for pharmaceutical formulations since the amount of the protein delivered for therapeutic use is critical. Accordingly, a protein concentration range of about 80 mg/ml to about 130 mg/ml would not be understood by one skilled in the art as to encompass a protein concentration at about 150 mg/ml.

In addition, there is no evidence in the specification indicating that the pH range of "about 4.2 to 5.3 or 6.5 to about 12.0" recited in claim 31 of the '432 patent encompasses a pH range of 5.5 to 6.0. As shown in the specification of the '432 patent, examples of pH include pH 4.0, 4.1, 4.2, ...5.3, and 6.5, 6.6, 6.7 ... 12.0. *See* col. 3, lines 17-48; col. 4, lines 35-67. The range from pH 5.5 to 6.0 is not listed as examples of the pH values. Figures 6 and 7 indicate that in the pH range of 5.5 to 6.0, the formulation had relatively higher viscosity. *See* Examples 6 and 7; and Figures 6 and 7. Thus, the pH range of "about 4.2 to 5.3 or 6.5 to about 12.0" does not encompass a pH range of 5.5 to 6.0. Further, as demonstrated in the Liu Declaration, a formulation having a pH ranging from 5.5 to 6.0 provides the advantage for maintaining stability of rhuMAbE25 in liquid formulations. This advantage for rhuMAbE25 liquid formulations was not appreciated by the '432 patent or the '243 publication.

Applicants disagree with the Examiner that obviousness-type double patenting is established since both claim sets encompass an antibody formulation comprising rhuMAb-E25 at 120-260 mg/ml in arginine-HCl, histidine, polysorbate at pH of 5.5-6.0. MPEP §804 II.B. provides that since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. §103(a) rejection, the factual inquiries set forth in *Graham v. John Deere*

Co., 383 U.S. 1, 148 USPQ 456 (1966) are employed when making an obvious-type double patenting analysis. MPEP §2144.08 further provides that the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *Citing In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). The same section of MPEP provides guidelines and factors that Office personnel should consider in determining whether a species or a subgenus is obvious over a genus. Applicants respectfully submit that for the reasons provided below, even if the claims cited in the '432 patent encompass an antibody formulation comprising about 150 m/ml to 260 mg/ml of rhuMAbE25, arginine-HCl (100 to 200 mM), histidine (10 to 100 mM), polysorbate (0.01 to 0.1%), and pH (from 5.5 to 6.0), claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of the '432 patent in view of the '243 publication.

Claims in the '432 patent do not teach or suggest that a specific combination of excipients for formulations comprising about 150 to 260 mg/ml rhuMAbE25, 100 to 200 mM arginine-HCl , 10 to 100 mM histidine, and 0.01 to 0,1% polysorbate, and a pH ranging from 5.5 to 6.0. The '243 publication does not cure this deficiency of the '432 patent. Although the '243 publication teaches using a combination of arginine and histidine for antibody liquid formulations, this reference only teaches use of a concentration for both arginine and histidine at 15 mM to 60 mM, and states that variations for histidine concentrations ranging from 15 mM to 60 mM and arginine concentrations from 15 mM to 60 mM did not affect the overall quality of the product (*i.e.*, antibody ABX-IL8). See Example 15, paragraph [0100]. As shown in the '432 patent, having higher salt concentration (such as arginine-HCl) in the formulation is important for reducing viscosity of the liquid formulation for rhuMAbE25. See Example 3 and Figure 3. This clearly demonstrates that rhuMAbE25 has properties different from antibody ABX-IL8; and one skilled in the art would not have been motivated to combine excipients disclosed in the '243 publication into the formulation claimed in the '432 patent for rhuMAbE25.

As argued in the response dated September 4, 2008, the Liu Declaration indicates that the turbidity problem for liquid formulations containing high concentration of rhuMAbE25 is unique to antibody rhuMAbE25. A skilled artisan would not be able to predict which excipient

would be effective for reducing turbidity. Neither the '432 patent nor the '243 publication appreciated the problem of turbidity for highly concentrated rhuMAbE25 formulations. Accordingly, based on the claims in the '432 patent and disclosures in the '243 publication, one skilled in the art would not have a reasonable expectation of success in producing the formulations for high concentrations of rhuMAbE25 (about 150 to 260 mg/ml) having reduced turbidity as claimed in the present application.

In view of the above, claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 51-56, 58 and 59 of the '432 patent in view of the '243 publication. Accordingly, Applicants respectfully request that this nonstatutory obviousness-type double patenting rejection be withdrawn.

B. Claims 1, 3-8, 20, 22-25, 51 and 52 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-27 of copending Application U.S.S.N. 12/197,005.

Applicants respectfully request that the rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending Application Ser. No. 12/197,005, at which time Applicants will address this issue.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392005600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 16, 2009

Respectfully submitted,

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